



Onquer



Patient Details

Sample ID	2507012255	Sample Collection Date	--/--/--
Sample Receiving Date	--/--/--	Sample Reporting Date	--/--/--

Analysis
Result
Range
Interpretation
Tumor Mutational Burden Score (TMB)

 0.37
mut/Mb

<5mut/Mb(Low TMB)

5-10 mut/Mb
(Intermediate TMB)

>10-20 mut/Mb (High
TMB)

Low TMB

Microsatellite Instability (MSI)

12%

<20%(MSI-L)

=20% (MSI-H)

No instability (MSS)

MSI-L

**Homologous Recombination
Deficiency Score (HRD)**

32

<42(Negative)

>=(Positive)

Negative

Results:

Sr. No.	Genomic Alteration	Associated FDA Approved Therapies (in this cancer type)	Clinical Trials
1	EGFR p.L858R Exon 21 Substitution (Please refer to page no. 3 for more details)	Osimertinib, Afatinib, Gefitinib, Erlotinib	(Please refer to page no 5)

Clinically relevant variant detected

Variant Summary						
Gene (Exon) [Transcript]	Variant (Amino acid Alteration)	Variant (Coding)	Variant Allele Frequency (VAF)	Variant Effect *	Variant Classification (AMP) **	Variant Classification (ACMG) #
EGFR (exon21) [NM_005228. 5]	p.Leu858Arg	c.2573T>G	46.5%	GOF	Tier 1	Pathogenic

*Variant effect: GOF: Gain of Function

**Four-Tiered Classification System based as per Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer, by Association for Molecular Pathology with liaison representation from the American College of Medical Genetics and Genomics, American Society of Clinical Oncology, and College of American Pathologists. [PMID: 27993330, 28157586]

Tier1: variants with strong clinical significance for therapy, prognosis and diagnosis for the same tumor type

Tier2: variants with potential clinical significance for therapy, prognosis and diagnosis for the different tumor type

Tier3: variants of unknown clinical significance (VUS)

Tier4: variants deemed benign or likely benign.

Five-Tiered Classification based on ACMG guidelines [PMID: 25741868]

Pathogenic, Likely Pathogenic, Variant of Unknown Significance (VUS), Likely Benign, Benign

FDA Approved Drug Indication

Drugs	Indication	Target Gene	Target Gene present in the current Indication	Clinical Trial (Current Indication) (Phase III/IV)
Afatinib	EGFR mutation positive NSCLC	Non-Resistant EGFR Mutations	EGFR p.Leu858Arg	Please refer to page no. 5 for more details
Dacomitinib	EGFR mutation positive NSCLC	EGFR exon 19 deletion EGFR p.Leu858Arg	EGFR p.Leu858Arg	
Erlotinib	EGFR mutation positive NSCLC	EGFR exon 19 deletion EGFR p.Leu858Arg	EGFR p.Leu858Arg	
Gefitinib	EGFR mutation positive NSCLC	EGFR exon 19 deletion EGFR p.Leu858Arg	EGFR p.Leu858Arg	
Osimertinib	EGFR mutation positive NSCLC	EGFR exon 19 deletion EGFR p.Leu858Arg EGFR p.Thr790Met	EGFR p.Leu858Arg	

Clinical Trials

Clinical Trial	Indication	Drug	Title	Phase	Status
NCT02716311	EGFR mutation positive NSCLC	Cetuximab Afatinib	Phase II Study Evaluating the Combination of Cetuximab With Afatinib as First-line Treatment for Patients With EGFR Mutated Non Small Cell Lung Cancer	II	Recruiting
NCT02633189	EGFR mutation positive NSCLC	Erlotinib	A Randomized Open-label Phase 3 Trial Comparing Bevacizumab + Erlotinib vs Erlotinib Alone as First Line Treatment of Patients With EGFR Mutated Advanced Non Squamous Non Small Cell Lung Cancer	III	Recruiting
NCT03521154	EGFR mutation positive NSCLC	Osimertinib	A Phase III, Randomized, Double-blind, Place-bo controlled, Multicenter, International Study of Osimertinib as Maintenance Therapy in Patients With Locally Advanced, Unresec-table EGFR Mutation-positive Non-Small Cell Lung Cancer (Stage III) Whose Disease Has Not Progressed Following Definitive Platinum-based Chemoradiation Therapy (LAURA)	III	Recruiting
NCT02511106	EGFR mutation positive NSCLC	Osimertinib	A Phase III, Double-blind, Randomized, Place-bo controlled Multi-centre, Study to Assess the Efficacy and Safety of AZD9291 Versus Placebo, in Patients With Epidermal Growth Factor Receptor Mutation Positive Stage IB-III A Non-small Cell Lung Carcinoma, Following Complete Tumor Resection With or Without Adjuvant Chemotherapy (ADAURA).	III	Recruiting

Variant Interpretation

EGFR: p.Leu858Arg(c.2573T>G)

Variant Annotation

The identified missense mutation, EGFR p.Leu858Arg, occurs in the tyrosine kinase domain within exon 21 of the EGFR gene and has shown to increase the kinase activity of the protein resulting in the constitutive activation of the receptor. This eventually leads to the ligand-independent activation of several downstream pathways such as the MAPK and PI3K-MTOR pathways, which are involved in several cellular processes such as cell proliferation, metastasis, and migration while preventing apoptosis. Thus, the EGFR p.Leu858Arg mutation is a gain of function mutation [MyCancerGenome, PMID: 19680293, 23172555, 30570396].

Gene Summary

The EGFR protein encoded by the EGFR gene is a transmembrane glycoprotein that is a member of the protein kinase superfamily. This protein is a receptor for members of the epidermal growth factor family. EGFR is a cell surface protein that binds to epidermal growth factor (EGF). The ligand (EGF) – receptor (EGFR) induces receptor dimerization and tyrosine autophosphorylation which leads to activation of the downstream signaling pathways that ultimately results in cell proliferation. Mutations in this gene are associated with lung cancer [Gene ID: 1956].

Variant incidence in disease

NSCLC remains the leading cause of cancer-related deaths globally. EGFR mutations which have been reported in ~35% of Asian population suffering from NSCLC. Specific EGFR, p.Leu858Arg mutation has been reported in ~43% of EGFR-mutated NSCLC [MyCancerGenome].

Clinical Relevance Of EGFR Inhibitors In Cancer

- A number of clinical and preclinical studies have reported significant antitumor activity with respect to prolonged survival with various first and second generation EGFR tyrosine kinase inhibitors, such as Erlotinib, Gefitinib, Afatinib etc. in EGFR mutated NSCLC, pancreatic and breast cancer patients as compared to patients with EGFR wild type tumors treated with chemotherapy [PMID:21670455,20573926,19692680,19826350].
- Additionally, third-generation EGFR TKIs such as Osimertinib, have shown encouraging results in metastatic NSCLC patients harbouring EGFR mutations including. Thr790Met mutation (that has shown to confer resistance to first and second generation EGFR TKIs) and who have progressed on prior TKI therapy [ASCO_Abstr 92336].
- Drugs such as Afatinib, Dacomitinib, Erlotinib, Gefitinib and Osimertinib have already gained FDA approval for use in EGFR mutated metastatic NSCLC patients.

Recommendations:

1. Genetic counseling is advised to interpret the potential consequences of the variant(s).
2. If results do not align with the clinical findings, additional testing should be considered based on the referring clinician's recommendation.
3. For confirmation of pathogenic variants, perform Sanger sequencing of the targeted region identified through preliminary screening and ensure bidirectional sequencing for accuracy.

Methodology:

1. Sample Collection and Extraction, Library Preparation and Sequencing was done by a partnered lab.
2. Data Analysis: We use a customized algorithm developed at Genomiki Solutions for data analysis. The algorithm integrates quality control, read alignment to the human reference genome (GRCh38) using BWA, and variant identification tailored to enhance accuracy and efficiency for genomic data interpretation.
3. Clinical Annotation: Variants are annotated based on their clinical relevance using data from published literature and in-house curated databases. These curated databases provide key information, including minor allele frequency, to enhance the accuracy and depth of the annotation process.

Limitations:

1. Genetic testing may not always provide definitive answers due to evolving medical knowledge and technology.
2. Accurate interpretation relies on comprehensive clinical and family history. Misinterpretation may arise if such information is incomplete.
3. Variations in coding regions that cannot be sequenced due to technological constraints may not be identified.
4. Mosaicism, rare technical errors or recent transfusions may impact result accuracy.
5. The results are based on the available medical knowledge at the time of analysis; if new evidence arises, reanalysis can be requested.

Disclaimer:

1. **Data Accuracy:** The interpretations are based on the quality of the input data. Inaccurate or degraded sample quality may impact results.
2. **Variant Classification:** Variants classified as "uncertain significance" should not be used as the sole basis for clinical decisions. Further research or testing may be necessary.
3. **Updates to Guidelines:** As scientific understanding evolves; variant classifications and interpretations may change. Regular updates to clinical reports may be necessary.
4. **Inheritance Patterns:** This report does not account for inheritance patterns unless explicitly analyzed and reported.
5. **Third-party Testing:** Results from this report should not be compared with those from other laboratories without proper reconciliation of methodologies.
6. **Scope of Testing:** This test analyzes only the regions of interest specified. Variants outside the tested regions are not detected and cannot be interpreted.
7. **Secondary Findings:** This test does not analyze or report on unrelated secondary findings unless explicitly included in the test scope.
8. **Laboratory Standards:** All analyses are performed by current quality control and quality assurance standards relevant to the laboratory's accreditation.
9. **Use of Computational Tools:** Computational predictions provided (if any) are adjunctive to clinical judgment and are not definitive.
10. **Counselling Recommendation:** Patients are strongly encouraged to seek genetic counselling to understand the results and implications.
11. **Non-diagnostic Nature:** This test does not comprehensively assess all genetic disorders or conditions.
12. **Data Sharing:** Results and anonymized data may be used for quality control or research purposes, adhering to applicable data privacy regulations.

References:

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